

REC'D 16 DEC 2004

WIPO PCT



**PRIORITY  
DOCUMENT**  
SUBMITTED OR TRANSMITTED IN  
COMPLIANCE WITH RULE 17.1(a) OR (b)

**Bescheinigung**

**Certificate**

**Attestation**

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten internationalen Patentanmeldung überein.

The attached documents are exact copies of the international patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet international spécifiée à la page suivante.

Den Haag, den  
The Hague,  
La Haye, le

15. 12. 2004

Der Präsident des Europäischen Patentamts  
Im Auftrag  
For the President of the European Patent Office  
Le Président de l'Office européen des brevets  
p. o.

Mrs. T. Bröcker-Tazelaar

Patentanmeldung Nr.  
Patent application no.  
Demande de brevet n°

PCT/EP 03/13072

BEST AVAILABLE COPY

**Blatt 2 der Bescheinigung**  
**Sheet 2 of the certificate**  
**Page 2 de l'attestation**

---

**Anmeldung Nr.:**  
**Application no.:**  
**Demande n°:**

PCT/EP 03/13072

**Anmelder:**  
**Applicant(s):**  
**Demandeur(s):**

1. ACTELION PHARMACEUTICAL LTD - Allschwil, Switzerland

**Bezeichnung der Erfindung:**  
**Title of the invention:**  
**Titre de l'invention:**

Novel Thiazolidin-4-one derivatives

**Anmeldetag:**  
**Date of filing:**  
**Date de dépôt:**

21 November 2003 (21.11.2003)

**In Anspruch genommene Priorität(en)**  
**Priority(ies) claimed**  
**Priorité(s) revendiquée(s)**

**Staat:**  
**State:**  
**Pays:**

**Tag:**  
**Date:**  
**Date:**

**Aktenzeichen:**  
**File no.**  
**Numéro de dépôt:**

**Benennung von Vertragsstaaten :** Siehe Formblatt PCT/RO/101 (beigefügt)  
**Designation of contracting states :** See Form PCT/RO/101 (enclosed)  
**Désignation d'états contractants :** Voir Formulaire PCT/RO/101 (ci-joint)

**Bemerkungen:**  
**Remarks:**  
**Remarques:**

## PCT REQUEST

Acteli 50/S1

Draft (NOT for submission) - printed on 20.11.2003 12:26:30 PM

III-3	<b>Applicant and/or inventor</b>	
III-3-1	This person is:	inventor only
III-3-4	Name (LAST, First)	MULLER, Claus
III-3-5	Address:	4, rue de Buschwiller F-68220 Hegenheim France
III-4	<b>Applicant and/or inventor</b>	
III-4-1	This person is:	inventor only
III-4-4	Name (LAST, First)	MATTHYS, Boris
III-4-5	Address:	Baumgartenstrasse 839 CH-4622 Egerkingen Switzerland
III-5	<b>Applicant and/or inventor</b>	
III-5-1	This person is:	inventor only
III-5-4	Name (LAST, First)	BINKERT, Christophe
III-5-5	Address:	In den Zieghoefen 89 CH-4054 Basel Switzerland
IV-1	<b>Agent or common representative; or address for correspondence</b> The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	
IV-1-1	Name (LAST, First)	agent  HOFMANN, Dieter
IV-1-2	Address:	Therwilerstrasse 87 CH-4153 Reinach Switzerland
IV-1-3	Telephone No.	+41 61 713 1560
IV-1-4	Facsimile No.	+41 61 713 1561
IV-1-5	e-mail	hofmannndrd@bluewin.ch
IV-1-5	Agent's registration No.	25510
V	<b>Designation of States</b>	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	--

5

## Novel thiazolidin-4-one derivatives

### Field of the invention

10 The present invention relates to novel thiazolidin-4-one derivatives of the General Formula (I) and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of the General Formula (I), and their use as immunosuppressant agents, either alone or in combination with other immunosuppressant therapies.

### 15 Background of the invention

The immune system attempts to fight a transplanted organ in the same way it fights an infection or a cancer. Without immunosuppressive medication to inhibit the immune system's action, a transplanted organ is quickly rejected and stops  
20 functioning. Organ transplant recipients can experience some organ rejection even when they are taking immunosuppressive drugs. Rejection occurs most frequently in the first few weeks after transplantation, but rejection episodes can also happen months or even years after transplantation. Combinations of up to three or four medications are commonly used to give maximum protection against rejection  
25 while minimizing side effects. Current standard drugs used to treat the rejection of transplanted organs interfere with discrete intracellular pathways in the activation of T-type or B-type white blood cells. Examples of such drugs are cyclosporin, daclizumab, basiliximab, everolimus, or FK506, which interfere with cytokine release or signaling; azathioprine or leflunomide, which inhibit nucleotide  
30 synthesis; or 15-deoxyspergualin, an inhibitor of leukocyte differentiation.

The beneficial effects of these therapies relate to their broad immunosuppressive effects; however, the generalized immunosuppression which these drugs produce also diminishes the immune system's defence against infection and malignancies. Furthermore, standard immunosuppressive drugs are often used at high dosages and can themselves cause or accelerate organ damage in either the transplanted organ itself, or in other target organs of the transplant recipient.

### **Description of the invention**

The present invention provides compounds having a powerful and long-lasting immunosuppressive effect which is achieved by reducing the number of circulating and infiltrating T- and B-lymphocytes, without affecting their maturation, memory, or expansion. In consequence, the compounds of the present invention can be utilized alone or in combination with standard T-cell activation inhibiting drugs, to provide a new immunosuppressive therapy with a reduced propensity for infections or malignancies when compared to standard immunosuppressive therapy. Furthermore, the compounds of the present invention can be used in combination with reduced dosages of traditional immunosuppressant therapies, to provide on the one hand effective immunosuppressive activity, while on the other hand reducing end organ damage associated with higher doses of standard immunosuppressive drugs.

The following paragraphs provide definitions of the various chemical moieties that make up the compounds according to the invention and are intended to apply uniformly throughout the specification and claims unless an otherwise expressly set out definition provides a broader definition.

The term **lower alkyl**, alone or in combination with other groups, means saturated, straight or branched chain groups with one to seven carbon atoms, preferably one to four carbon atoms. Examples of lower alkyl groups are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *n*-hexyl or *n*-heptyl.

The term **lower alkoxy** means a R-O group, wherein R is a lower alkyl. Preferred examples of lower alkoxy groups are methoxy, ethoxy, propoxy, iso-propoxy, *iso*-butoxy, *sec*-butoxy or *tert*-butoxy.

- 5 The term **mono- or di-lower alkylamino** means a R'-NH- or a R'-NR''- group, wherein R' and R'' are each independently a lower alkyl. Preferred examples of mono- or di-lower alkylamino groups are methylamino, ethylamino, N,N-dimethylamino, or N-methyl-N-ethyl-amino.
- 10 The term **lower alkenyl**, alone or in combination with other groups, means straight or branched chain groups comprising an olefinic bond and three to seven carbon atoms, preferably three to five carbon atoms. Examples of lower alkenyl are allyl, (E)-but-2-enyl, (Z)-but-2-enyl, or but-3-enyl.
- 15 The term **lower alkynyl**, alone or in combination with other groups, means straight or branched chain groups comprising a triple bond and three to seven carbon atoms, preferably three to four carbon atoms. Examples of lower alkynyl are prop-2-ynyl or but-3-ynyl.
- 20 The term **halogen** means fluoro, chloro, bromo or iodo.

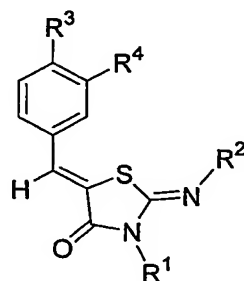
- The term **cycloalkyl** alone or in combination, means a saturated cyclic hydrocarbon ring system with 3 to 7 carbon atoms, preferably three to five carbon atoms. Examples of cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl
- 25 or cycloheptyl.

- The expression **pharmaceutically acceptable salts** encompasses either salts with inorganic acids or organic acids like hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid,
- 30 benzoic acid, methanesulfonic acid, p-toluenesulfonic acid, and the like that are non-toxic to living organisms. In case the compound of General Formula (I) or General Formula (II) is acidic in nature the expression encompasses salts with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium

hydroxide, calcium hydroxide, and the like which are also non-toxic to living organisms.

The compounds of the General Formula (I) and General Formula (II) can contain one or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and meso-forms. The present invention encompasses all these forms.

- 10 A first aspect of the invention consists of a novel pharmaceutical composition comprising at least one thiazolidin-4-one derivative of the General Formula (I):



General Formula (I)

- 15 wherein:

R<sup>1</sup> represents lower alkyl, lower alkenyl; lower alkynyl; cycloalkyl;  $\alpha$ -naphthyl;  $\beta$ -naphthyl; 5,6,7,8-tetrahydronaphth-1-yl; 5,6,7,8-tetrahydronaphth-2-yl; a phenyl group; a phenyl group independently mono-, di- or trisubstituted with lower alkyl, halogen, lower alkoxy, -CF<sub>3</sub>, or -CN;

R<sup>2</sup> represents lower alkyl; allyl; cyclopropyl; cyclobutyl; cyclopentyl; mono- or di-lower alkylamino;

- 25 R<sup>3</sup> represents -NR<sup>5</sup>R<sup>6</sup>; -O-CR<sup>7</sup>R<sup>8</sup>-CR<sup>9</sup>R<sup>10</sup>-(CR<sup>11</sup>R<sup>12</sup>)<sub>n</sub>-O-R<sup>13</sup>;

$R^4$  represents hydrogen; hydroxy; lower alkoxy; lower alkyl; halogen; or  $R^3$  and  $R^4$  together may form a methylenedioxy or ethylenedioxy ring which may be further substituted with a hydroxy methyl group;

5  $R^5$  and  $R^6$  each represents independently lower alkyl;

$R^7$  represents hydrogen, lower alkyl or hydroxymethyl;  $R^7$  and  $R^9$  together with the carbon atoms to which they are attached may form a five- or six-membered saturated carbocyclic ring; in case  $n$  represents the integer 1,  $R^7$  and  $R^{11}$  together  
10 with the carbon atoms to which they are attached may form a five- or six-membered saturated carbocyclic ring;

$R^8$ ,  $R^9$ ,  $R^{11}$  and  $R^{12}$  each represents independently hydrogen or lower alkyl;

15  $R^{10}$  represents hydrogen or lower alkyl; in case  $n$  represents the integer 1,  $R^{10}$  in addition represents lower alkoxy, hydroxy,  $-NH_2$ ,  $-NHR^5$  or  $-NR^5R^6$ ;

$R^{13}$  represents hydrogen; lower alkyl; hydroxycarbonyl-lower alkyl;  $-(CH_2)_2-OH$ ; 1-glyceryl or 2-glyceryl;

20

$n$  represents the integer 0 or 1;

and configurational isomers, optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric  
25 racemates, mixtures of diastereomeric ~~racemates~~ and the meso-form, as well as pharmaceutically acceptable salts, solvent complexes, and morphological forms, and inert carrier material.

The compounds of General Formula (I) and their pharmaceutically acceptable  
30 salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parental or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the

form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions, or topically, e.g. in the form of ointments, cream or oils.

The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art (see for example Mark Gibson, Editor, Pharmaceutical Preformulation and Formulation, IHS Health Group, Englewood, CO, USA, 2001; Remington, The Science and Practice of Pharmacy, 20th Edition, Philadelphia College of Pharmacy and Science) by bringing the described compounds of General Formula (I) and their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable inert carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers are, however, required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of General Formula (I) can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 0.5 mg to about 1000 mg, especially about 1 mg to about 500 mg, comes into consideration for the treatment of disorders associated with an activated immune system for adult patients. Depending on the dosage it may be convenient to administer the daily dosage in several dosage units.

The pharmaceutical preparations conveniently contain about 0.5 to 500 mg, preferably 1 to 250 mg, of a compound of General Formula (I).

In a preferred embodiment according to the invention, the above-mentioned pharmaceutical composition comprises the (Z, Z)-isomers of the thiazolidin-4-one derivatives of the General Formula (I).

The above-mentioned pharmaceutical composition is useful for the prevention and treatment of disorders associated with an activated immune system.

Such diseases or disorders are selected from the group consisting of rejection of transplanted organs or tissue; graft-versus-host diseases brought about by transplantation; autoimmune syndromes including rheumatoid arthritis; systemic lupus erythematosus; Hashimoto's thyroiditis; lymphocytic thyroiditis; multiple sclerosis; myasthenia gravis; type I diabetes; uveitis; posterior uveitis; uveitis associated with Behcet's disease; uveomeningitis syndrome; allergic encephalomyelitis; chronic allograft vasculopathy; post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis; inflammatory and hyperproliferative skin diseases; psoriasis; atopic dermatitis; osteomyelitis; contact dermatitis; eczematous dermatitis; seborrheic dermatitis; lichen planus; pemphigus; bullous pemphigoid; epidermolysis bullosa; urticaria; angioedema; vasculitis; erythema; cutaneous eosinophilia; acne; alopecia areata; keratoconjunctivitis; vernal conjunctivitis; keratitis; herpetic keratitis; dystrophia epithelialis corneae; corneal leukoma; ocular pemphigus; Mooren's ulcer;

ulcerative keratitis; scleritis; Graves' ophthalmopathy; Vogt-Koyanagi-Harada  
 syndrome; sarcoidosis; pollen allergies; reversible obstructive airway disease;  
 bronchial asthma; allergic asthma; intrinsic asthma; extrinsic asthma; dust asthma;  
 chronic or inveterate asthma; late asthma and airway hyper-responsiveness;  
 5 bronchitis; gastric ulcers; ischemic bowel diseases; inflammatory bowel diseases;  
 necrotizing enterocolitis; intestinal lesions associated with thermal burns; coeliac  
 diseases; proctitis; eosinophilic gastroenteritis; mastocytosis; Crohn's disease;  
 ulcerative colitis; vascular damage caused by ischemic diseases and thrombosis;  
 atherosclerosis; fatty heart; myocarditis; cardiac infarction; arteriosclerosis; aortitis  
 10 syndrome; cachexia due to viral disease; vascular thrombosis; migraine; rhinitis;  
 eczema; interstitial nephritis; IgA-induced nephropathy; Goodpasture's syndrome;  
 hemolytic-uremic syndrome; diabetic nephropathy; glomerulosclerosis;  
 glomerulonephritis; multiple myositis; Guillain-Barre syndrome; Meniere's disease;  
 polyneuritis; multiple neuritis; mononeuritis; radiculopathy; hyperthyroidism;  
 15 Basedow's disease; thyrotoxicosis; pure red cell aplasia; aplastic anemia;  
 hypoplastic anemia; idiopathic thrombocytopenic purpura; autoimmune hemolytic  
 anemia; agranulocytosis; pernicious anemia; megaloblastic anemia;  
 anerythroplasia; osteoporosis; sarcoidosis; fibroid lung; idiopathic interstitial  
 pneumonia; dermatomyositis; leukoderma vulgaris; ichthyosis vulgaris;  
 20 photoallergic sensitivity; cutaneous T cell lymphoma; polyarteritis nodosa;  
 Huntington's chorea; Sydenham's chorea; myocardosis; scleroderma; Wegener's  
 granuloma; Sjogren's syndrome; adiposis; eosinophilic fascitis; lesions of gingiva,  
 periodontium, alveolar bone, substantia ossea dentis; male pattern alopecia or  
 alopecia senilis; muscular dystrophy; pyoderma; Sezary's syndrome; chronic  
 25 adrenal insufficiency; Addison's disease; ischemia-reperfusion injury of organs  
 which occurs upon preservation; endotoxin shock; pseudomembranous colitis;  
 colitis caused by drug or radiation; ischemic acute renal insufficiency; chronic renal  
 insufficiency; lung cancer; malignancy of lymphoid origin; acute or chronic  
 lymphocytic leukemias; lymphoma; psoriasis; pulmonary emphysema; cataracta;  
 30 siderosis; retinitis pigmentosa; senile macular degeneration; vitreal scarring;  
 corneal alkali burn; dermatitis erythema; ballous dermatitis; cement dermatitis;  
 gingivitis; periodontitis; sepsis; pancreatitis; carcinogenesis; metastasis of  
 carcinoma; hypobaropathy; autoimmune hepatitis; primary biliary cirrhosis;

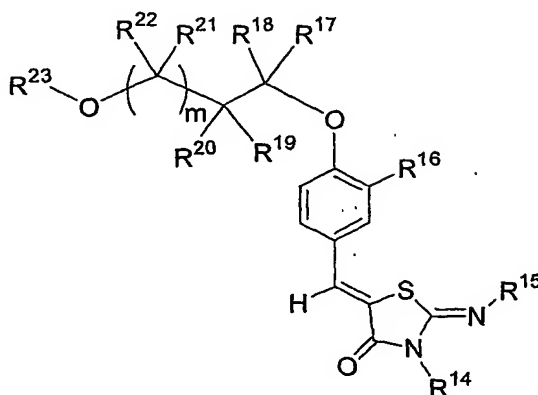
sclerosing cholangitis; partial liver resection; acute liver necrosis; cirrhosis; alcoholic cirrhosis; hepatic failure; fulminant hepatic failure; late-onset hepatic failure; "acute-on-chronic" liver failure.

- 5 Particularly preferred diseases comprise the group consisting of rejection of transplanted organs or tissue; graft-versus-host diseases brought about by transplantation; autoimmune syndromes including rheumatoid arthritis, multiple sclerosis, myasthenia gravis; pollen allergies; type I diabetes; prevention of psoriasis; Crohn's disease; post-infectious autoimmune diseases including  
10 rheumatic fever and post-infectious glomerulonephritis; and metastasis of carcinoma.

Furthermore, compounds of the General Formula (I) are also useful, in combination with one or several immunosuppressant agents, for the treatment of  
15 disorders associated with an activated immune system and selected from the list as above-mentioned. According to a preferred embodiment of the invention, said immunosuppressant agent is selected from the group comprising or consisting of cyclosporin, daclizumab, basiliximab, everolimus, tacrolimus (FK506), azathioprine, leflunomide, 15-deoxyspergualin, or other immunosuppressant  
20 drugs.

Another aspect of the invention concerns a method for the prevention or treatment of disorders associated with an activated immune system comprising the administration to the patient of a pharmaceutical composition containing a  
25 compound of the General Formula (I). A suitable dose of the compound of General Formula (I) in the pharmaceutical composition is between 0.5 mg and 1000 mg per day. In a preferred embodiment of the invention, said dose is comprised between 1 mg and 500 mg per day and more particularly between 5 mg and 200 mg per day.

A further aspect of the invention are novel thiazolidin-4-one derivatives of the following General Formula (II):



General Formula (II)

wherein:

$R^{14}$  represents lower alkyl, lower alkenyl; lower alkynyl; cycloalkyl;  $\alpha$ -naphthyl;  $\beta$ -naphthyl; 5,6,7,8-tetrahydronaphth-1-yl; 5,6,7,8-tetrahydronaphth-2-yl; a phenyl group; a phenyl group mono-, di- or trisubstituted independently with lower alkyl, halogen, lower alkoxy,  $-CF_3$ , or  $-CN$ ;

$R^{15}$  represents lower alkyl; allyl; cyclopropyl; cyclobutyl; cyclopentyl; mono- or di-lower alkylamino;

$R^{16}$  represents hydrogen; hydroxy; lower alkoxy; lower alkyl or halogen;

$R^{17}$  represents hydrogen, lower alkyl, or hydroxymethyl;  $R^{17}$  and  $R^{19}$  together with the atoms to which they are attached may form a five- or six-membered carbocyclic saturated ring; in case  $m$  represents the integer 1,  $R^{17}$  and  $R^{21}$  together with the atoms to which they are attached may form a five- or six-membered carbocyclic saturated ring;

$R^{18}$ ,  $R^{19}$ ,  $R^{21}$  and  $R^{22}$  each represents independently hydrogen or lower alkyl;

$R^{20}$  represents hydrogen or lower alkyl; and in case  $m$  represents the integer 1,  $R^{20}$  in addition represents lower alkoxy, hydroxy,  $-NH_2$ ,  $-NHR^5$  or  $-NR^5R^6$ ;

$R^{23}$  represents hydrogen; lower alkyl; hydroxycarbonyl-lower alkyl;  $-(CH_2)_2-OH$ ;  
5 1-glyceryl or 2-glyceryl;

$m$  represents the integer 0 or 1;

and configurational isomers, optically pure enantiomers, mixtures of enantiomers  
10 such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form, as well as pharmaceutically acceptable salts.

Preferred thiazolidin-4-one derivatives according to General Formula (II) are (Z,Z)  
15 isomers of General Formula (II).

In a preferred embodiment,  $R^{14}$  represents an unsubstituted, a mono- or disubstituted phenyl group.

20 In a further preferred embodiment,  $R^{15}$  represents lower alkyl.

In another preferred embodiment,  $m$  represents the integer 0; and  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$  and  $R^{20}$  represent hydrogen.

25 In a particularly preferred embodiment,  $R^{23}$  represents hydrogen.

In a more particularly preferred embodiment,  $R^{16}$  represents hydrogen, halogen or methyl.

30 In another particularly preferred embodiment,  $R^{14}$  represents an unsubstituted, a mono- or disubstituted phenyl group;  $R^{15}$  represents lower alkyl;  $m$  represents the integer 0;  $R^{16}$  represents hydrogen, halogen or methyl; and  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{23}$  each represent hydrogen.

In another preferred embodiment, m represents the integer 1,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{21}$ ,  $R^{22}$ ,  $R^{23}$  represent hydrogen, and  $R^{20}$  represents hydroxy.

5 Specific thiazolidin-4-one derivatives according to formula (II) are:

5-[4-(2-Hydroxy-ethoxy)-benz-(Z)-ylidene]-2-[(Z)-isopropylimino]-3-o-tolyl-thiazolidin-4-one;

10 3-(2,3-Dimethyl-phenyl)-5-[4-(2-hydroxy-ethoxy)-benz-(Z)-ylidene]-2-[(Z)-isopropylimino]-thiazolidin-4-one;

5-[4-(2-Hydroxy-ethoxy)-benz-(Z)-ylidene]-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one;

15

5-[3-Chloro-4-(2-hydroxy-ethoxy)-benz-(Z)-ylidene]-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one;

20

5-[3-Chloro-4-(2-hydroxy-ethoxy)-benz-(Z)-ylidene]-2-[(Z)-isopropylimino]-3-(2-methylphenyl)-thiazolidin-4-one;

5-[3-Chloro-4-(2-hydroxy-ethoxy)-benz-(Z)-ylidene]-3-(2,3-dimethyl-phenyl)-2-[(Z)-isopropylimino]-thiazolidin-4-one;

25

5-[4-(2-Hydroxy-ethoxy)-benz-(Z)-ylidene]-3-phenyl-2-[(Z)-propylimino]-thiazolidin-4-one;

5-[3-Chloro-4-(2-hydroxy-ethoxy)-benz-(Z)-ylidene]-3-(2,3-dimethyl-phenyl)-2-[(Z)-propylimino]-thiazolidin-4-one;

30

5-[3-Chloro-4-(2,3-dihydroxy-propoxy)-benz-(Z)-ylidene]-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one;

5-[3-Chloro-4-(2,3-dihydroxy-propoxy)-benz-(Z)-ylidene]-2-[(Z)-isopropylimino]-3-o-  
tolyl-thiazolidin-4-one;

5 [5-[3-Chloro-4-(2,3-dihydroxy-propoxy)-benz-(Z)-ylidene]-3-(2,3-dimethyl-phenyl)-2-  
[(Z)-isopropylimino]-thiazolidin-4-one;

5-[3-Chloro-4-(2,3-dihydroxy-propoxy)-benz-(Z)-ylidene]-3-phenyl-2-[(Z)-propyl-  
imino]-thiazolidin-4-one;

10 5-[3-Chloro-4-(2,3-dihydroxy-propoxy)-benz-(Z)-ylidene]-2-[(Z)-propylimino]-3-o-  
tolyl-thiazolidin-4-one;

5-[3-Chloro-4-(2,3-dihydroxy-propoxy)-benz-(Z)-ylidene]-3-(2,3-dimethyl-phenyl)-2-  
[(Z)-propylimino]-thiazolidin-4-one,

15

5-[3-Chloro-4-(2-hydroxy-ethoxy)-benz-(Z)-ylidene]-3-isopropyl-2-[(Z)-isopropyl-  
imino]-thiazolidin-4-one.

20 Compounds of General Formula (I) and General Formula (II) are suitable for the  
use as medicament.

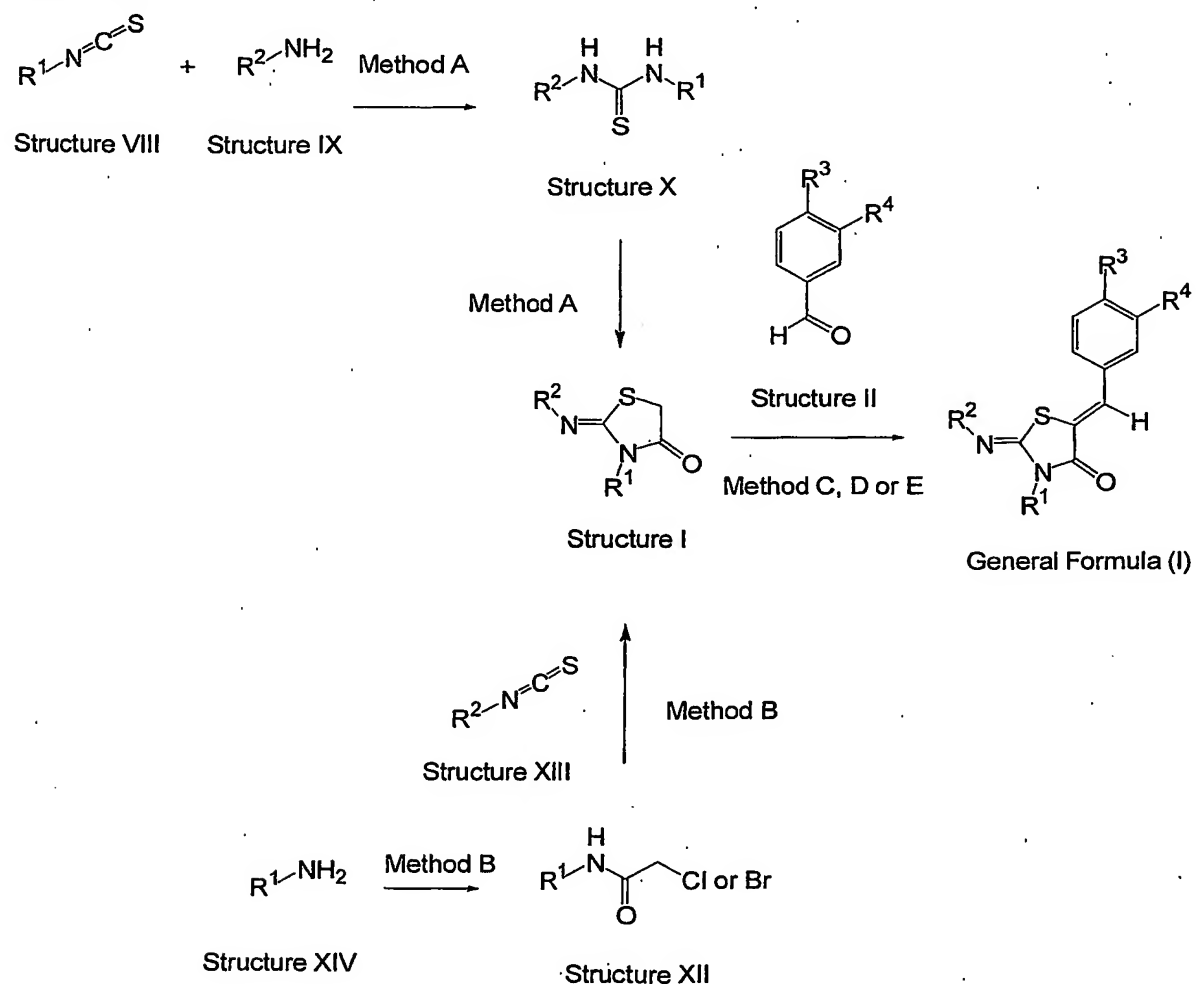
Still a further object of the present invention is a process to prepare a  
pharmaceutical composition comprising a compound of the General Formula (I) or  
a compound of the General Formula (II) by mixing one or more active ingredients  
25 with inert excipients in a manner known *per se*.

The compounds of General Formulae (I) and (II) can be manufactured by the  
methods given below, by the methods given in the Examples or by analogous  
methods. Optimum reaction conditions may vary with the particular reactants or  
30 solvents used, but such conditions can be determined by a person skilled in the art  
by routine optimisation procedures.

Compounds of the General Formula (I) and General Formula (II) of the present invention can be prepared according to the general sequence of reactions outlined below. Only a few of the synthetic possibilities leading to compounds of General Formula (I) and General Formula (II) are described as summarized in Scheme 1.

5

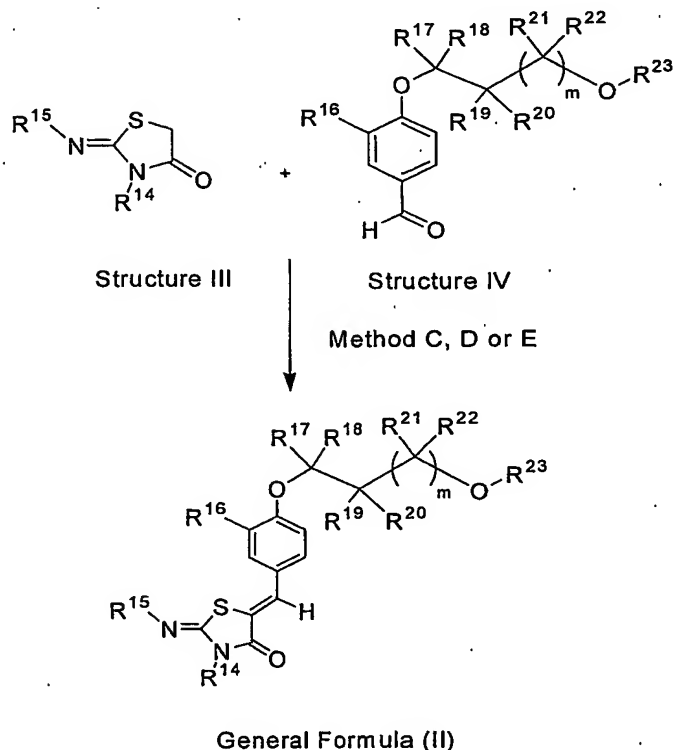
### Scheme 1



According to Scheme 1, compounds of the General Formula (I) can be prepared by reacting a compound of Structure I with a compound of Structure II, for instance, in acetic acid at elevated temperatures and in the presence of a base such as sodium acetate. The reaction can also be carried out in a non-polar solvent such as toluene or benzene in the presence of an amine such as pyrrolidine or piperidine.

Likewise, compounds of the General Formula (II) can be prepared by reacting a compound of Structure III with a compound of Structure IV (Scheme 2).

### Scheme 2

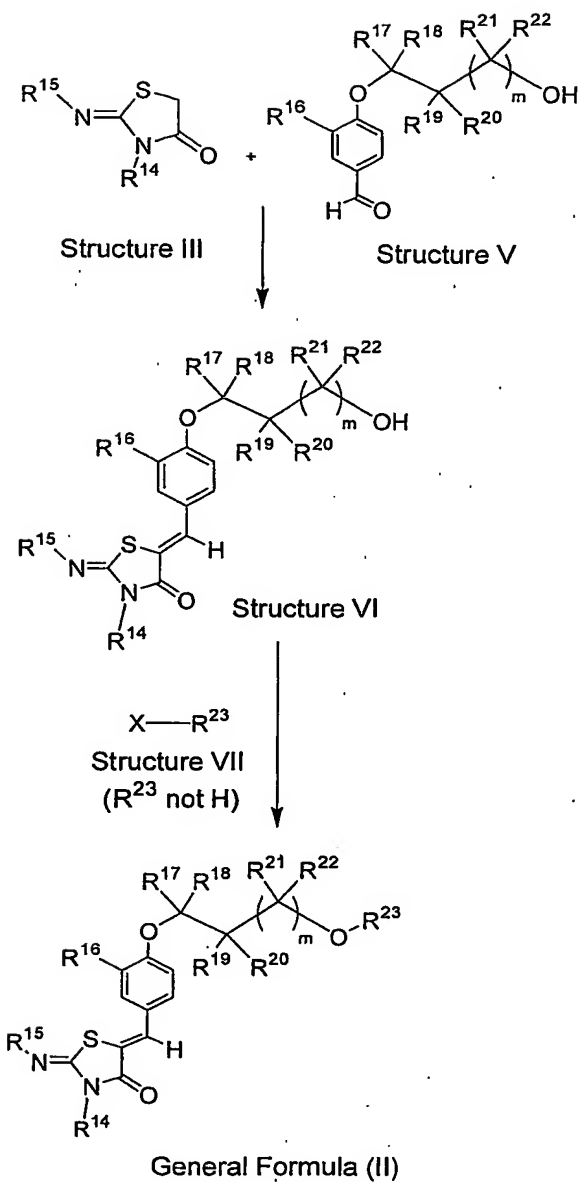


5

Depending on the nature of  $R^{23}$ , it may be beneficial to prepare the compounds of General Formula (II) by first reacting a compound of Structure III with the compound of Structure V to form a compound of Structure VI (Scheme 3). The compound of Structure VI is then treated with a compound of Structure VII wherein X represents a leaving group such a chlorine, a bromine or an iodine atom, or a sulfonic acid ester group in the presence of a base such as  $K_2CO_3$ , NaH, or triethylamine in a solvent such as THF, DMF, acetone, or DMSO.

15

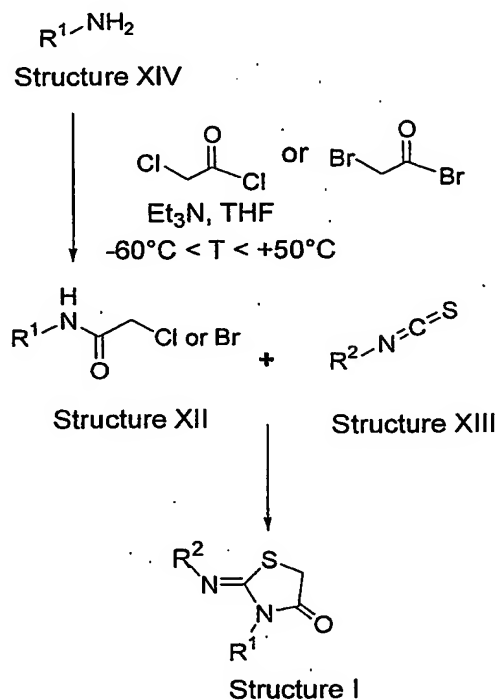
### Scheme 3



As outlined in Scheme 1, the compounds of Structure I can be prepared by reacting a compound of Structure VIII with a compound of Structure IX to form the intermediate of Structure X which is then cyclised to the compound of Structure I with a bromo- or chloroacetic acid ester of Structure XI. This reaction is ideally performed in a two step-one pot procedure at room temperature using an alcohol such as methanol or ethanol as solvent. The second step can be catalysed by the addition of pyridine.

Alternatively, the compounds of Structure I can also be prepared by reacting a compound of Structure XII with a compound of Structure XIII in the presence of a base such as NaH in a solvent such as THF or DMF. Compounds of the Structure XII are prepared by treating a compound of Structure XIV with chloroacetic acid chloride or bromoacetic acid bromide in a solvent such as THF, DMF or DCM in the presence of a base such as triethylamine, ethyldiisopropylamine at temperatures between -60 and +50°C (Scheme 4).

#### Scheme 4



The preparation of compounds of Structure III is in analogy to the preparation of compounds of Structure I.

## Examples

The following examples illustrate the invention but do not at all limit the scope thereof.

5

All temperatures are stated in °C. Compounds are characterized by <sup>1</sup>H-NMR (300MHz) or <sup>13</sup>C-NMR (75MHz) (Varian Oxford; chemical shifts are given in ppm relative to the solvent used; multiplicities: s = singlet, d = doublet, t = triplet; p = pentuplet, hex = hexet, hept = heptet, m = multiplet, br = broad, coupling constants are given in Hz); by LC-MS (Finnigan Navigator with HP 1100 Binary Pump and DAD, column: 4.6x50 mm, Zorbax SB-AQ, 5 m, 120A, gradient: 5-95% acetonitrile in water, 1 min, with 0.04% trifluoroacetic acid, flow: 4.5 ml/min), t<sub>R</sub> is given in min; by TLC (TLC-plates from Merck, Silica gel 60 F<sub>254</sub>); or by melting point. Compounds are purified by preparative HPLC (column: Grom Saphir Rp-C<sub>18</sub>, 110A, 5 m, 30x30 mm, gradient: 10-95% acetonitrile in water containing 0.5 % of formic acid, in 2 min, flow: 75 mL/min) or by MPLC (Labomatic MD-80-100 pump, Linear UVIS-201 detector, column: 350x18 mm, Labogel-RP-18-5s-100, gradient: 10% methanol in water to 100% methanol).

## 20 Abbreviations

aq.	aqueous
atm	atmosphere
DCM	dichloromethane
DMF	dimethylformamide
25 DMSO	dimethylsulfoxide
EA	ethyl acetate
h	hour
Hex	hexane
HV	high vacuum conditions
30 min	minutes
THF	tetrahydrofuran
rt	room temperature

sat.	saturated
$t_R$	retention time
tlc	thin layer chromatography

5 Typical procedure for the preparation of the 2-imino-thiazolidin-4-one scaffold (Method A)

To a solution of isopropylamine (1.31 g, 22.19 mmol) in methanol (25 mL) is added portionwise phenylisothiocyanate (3.0 g, 22.19 mmol). The solution which becomes slightly warm during the addition is stirred at rt for 4 h before pyridine  
 10 (2.63 g, 33.29 mmol) and methyl bromoacetate (3.39 g, 22.19 mmol) is added. The mixture is stirred for another 16 h at rt before it is poured onto 1 N aq. HCl (100 mL) and extracted with diethyl ether (150 mL). The aq. layer is neutralised by adding sat. aq. NaHCO<sub>3</sub> and extracted with diethyl ether (4x150 mL). The organic  
 15 extracts are dried over MgSO<sub>4</sub> and evaporated. The remaining solid is suspended in diethyl ether/heptane, filtered off, washed with additional diethyl ether/heptane and dried to give 3-phenyl-2-[(Z)-isopropylimino]-thiazolidin-4-one.

Typical procedure for the preparation of the 2-imino-thiazolidin-4-one scaffold (Method B)

20 a) A solution of aniline (9.31 g, 100 mmol) and triethylamine (15.2 g, 150 mmol) in THF (150 mL) is cooled to -40°C before chloroacetic acid chloride (11.3 g, 100 mmol) is slowly added in portions such that the temperature does not rise above 0°C. After completion of the addition, the brown suspension is stirred at rt for 1 h. The dark purple mixture is poured onto water (300 mL) and extracted twice with  
 25 EA (300 mL). The organic extracts are washed with sat. aq. NaHCO<sub>3</sub>, 0.5 N aq. HCl, followed by water, and evaporated. The brown residue is suspended in diethyl ether, filtered off, washed with additional diethyl ether and dried under high vacuum to give 2-chloro-N-phenyl-acetamide.

LC-MS:  $t_R$  = 0.75 min,  $[M+1]^+$  = 170

30 <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.22 (s br, 1H), 7.56-7.51 (m, 2H), 7.40-7.24 (m, 2H), 7.20-7.14 (m, 1H), 4.20 (s, 2H).

b) At rt, NaH (154 mg of 55% dispersion in mineral oil, 3.54 mmol) is added in portions to a solution of n-propylisothiocyanate (596 mg, 5.90 mmol) and the above 2-chloro-N-phenyl-acetamide (1000 mg, 5.90 mmol) in DMF (30 mL). Stirring is continued for 2 h after completion of the addition. The mixture is poured  
 5 onto EA (150 mL) and is extracted twice with 1 N aq. HCl (200 mL). The aq. layer is neutralised by adding 3 N NaOH followed by sat. aq. NaHCO<sub>3</sub>, and extracted twice with EA (200 mL). The organic extracts are washed with water (200 mL) and evaporated to give a pale yellow, crystalline solid. This material is suspended in a small amount of diethyl ether/hexane 1:1, filtered, washed with additional diethyl  
 10 ether/hexane and dried under high vacuum to give 3-phenyl-2-[(Z)-propylimino]-thiazolidin-4-one.

Typical procedure for the introduction of the benzylidene substituent (Method C)

A solution of 3-phenyl-2-[(Z)-isopropylimino]-thiazolidin-4-one (150 mg, 0.64  
 15 mmol), piperonal (192 mg, 1.28 mmol) and sodium acetate (105 mg, 1.28 mmol) in acetic acid (3 mL) is stirred at 110°C for 4 h. The dark yellow to brown solution is cooled to rt, diluted with EA (75 mL), washed with sat. aq. NaHCO<sub>3</sub>, followed by water, and evaporated. The crude product is purified by crystallisation from a small amount of methanol (approx. 5mL) to give 5-benzo[1,3]dioxol-5-ylmeth-(Z)-  
 20 ylidene-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one.

Typical procedure for the introduction of the benz-(Z)-ylidene substituent (Method D)

A solution of 3-phenyl-2-[(Z)-isopropylimino]-thiazolidin-4-one (150 mg, 0.64  
 25 mmol), 4-(2-hydroxyethoxy)benzaldehyde (213 mg, 1.28 mmol) and sodium acetate (105 mg, 1.28 mmol) in acetic acid (3 mL) is stirred at 110°C for 3 h. The brown solution is cooled to rt, diluted with EA (75 mL), washed with sat. aq. NaHCO<sub>3</sub>, followed by water, and evaporated. The residue is dissolved in methanol (20 mL) and sodium methylate is added (150 mg). The resulting solution is allowed  
 30 to stand for 40 min at rt before it is diluted with EA, washed with 10% aq. citric acid, and twice with water. The organic extracts are evaporated and the residue is crystallised from methanol to give (2Z, 5Z)-3-phenyl-5-[4-(2-hydroxy-ethoxy)-benz-(Z)-ylidene]-2-[(Z)-isopropylimino]-thiazolidin-4-one.

Typical procedure for the introduction of the benz-(Z)-ylidene substituent (Method E)

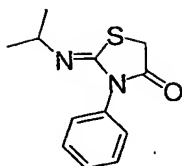
A solution of 3-(2-methylphenyl)-2-[(Z)-isopropylimino]-thiazolidin-4-one (50 mg, 0.200 mmol), 2,3-dihydro-benzo[1,4]dioxine-6-carbaldehyde (49 mg, 0.300 mmol) and sodium acetate (33 mg, 0.400 mmol) in acetic acid (1 mL) is stirred at 110°C for 5 h. The reaction mixture is cooled to rt and subjected to prep. HPLC purification. The product containing fractions are evaporated and dried to give 5-(2,3-dihydro-benzo[1,4]dioxin-6-ylmeth-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-o-tolyl-thiazolidin-4-one.

Preparation of 4-(3-hydroxy-propoxy)-benzaldehyde:

To a solution of 3-(4-hydroxymethylphenoxy)propionic acid (4.00 g, 20.40 mmol) in THF (20 mL) is added a solution of LiAlH<sub>4</sub> (10 mL, 1 M in THF). The mixture becomes warm and is diluted with THF (20 mL) before it is refluxed. After 1 and 2 h two further portions of LiAlH<sub>4</sub> (2x10 mL, 1 M in THF) are added. The mixture is refluxed overnight, cooled to rt and carefully quenched by the addition of water (1.2 g), 15% aq. NaOH (1.2 g) and water (3.2 g). The white precipitate is filtered off, and the filtrate is evaporated and dried to give 3-(4-hydroxymethyl-phenoxy)-propan-1-ol.

<sup>1</sup>H NMR (D<sub>6</sub>-DMSO): δ 7.21-7.15 (m, 2H), 6.86-6.81 (m, 2H), 5.00 (t, J = 5.9 Hz, 1H), 4.51 (t, J = 5.3 Hz, 1H), 4.39 (d, J = 5.3 Hz, 2H), 3.99 (t, J = 6.4 Hz, 2H), 3.57-3.50 (m, 2H), 1.83 (p, J 0 6.4 Hz, 2H). To a suspension of the above 3-(4-hydroxymethyl-phenoxy)-propan-1-ol (1.50 g, 8.23 mmol) in acetonitrile (25 mL) is added N-methylmorpholine-N-oxide (1.50 g, 12.38 mmol) followed by tetrapropylammonium perruthenate (140 mg, 0.43 mmol). The dark solution is stirred at rt for 2 h before the solvent is removed in vacuo. The crude product is purified by column chromatography on silica gel (heptane/EA) to give 4-(3-hydroxy-propoxy)-benzaldehyde.

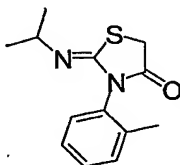
<sup>1</sup>H NMR (D<sub>6</sub>-DMSO): δ 9.83 (s, 1H), 7.85-7.81 (m, 2H), 7.12-7.07 (m, 2H), 4.56 (t, J = 5.3 Hz, 1H), 4.14 (t, J = 6.4 Hz, 2H), 3.57-3.51 (m, 2H), 1.88 (p, J = 6.4 Hz, 2H).

Scaffold 1

2-[(Z)-Isopropylimino]-3-phenyl-thiazolidin-4-one is prepared as described in

5 Method A. LC-MS:  $t_R = 0.58$  min,  $[M+1]^+ = 235$ .

$^1H$  NMR ( $CDCl_3$ ):  $\delta$  7.50-7.36 (m, 3H), 7.29-7.24 (m, 2H), 3.98 (s, 2H), 3.51 (hept,  $J = 6.4$  Hz, 1H), 1.14 (d,  $J = 5.9$  Hz, 6H).

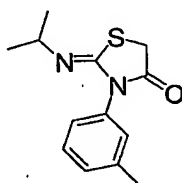
Scaffold 2

10

2-[(Z)-Isopropylimino]-3-o-tolyl-thiazolidin-4-one is obtained following Method A and starting from o-tolylisothiocyanate (3.0 g, 20.10 mmol), isopropylamine (1.19 g, 20.10 mmol), and methyl bromoacetate (3.08 g, 20.1 mmol).

15 LC-MS:  $t_R = 0.67$  min,  $[M+1]^+ = 249$ .

$^1H$  NMR ( $CDCl_3$ ):  $\delta$  7.34-7.26 (m, 3H), 7.14-7.08 (m, 1H), 4.00 (s, 2H), 3.50 (hept,  $J = 6.4$  Hz, 1H), 2.16 (s, 3H), 1.12 (d,  $J = 6.4$  Hz, 3H), 1.11 (d,  $J = 6.4$  Hz, 3H).

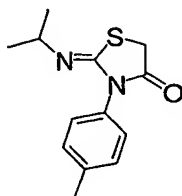
Scaffold 3

20

2-[(Z)-Isopropylimino]-3-m-tolyl-thiazolidin-4-one is obtained following Method A and starting from m-tolylisothiocyanate (3.0 g, 20.10 mmol), isopropylamine (1.19 g, 20.10 mmol), and methyl bromoacetate (3.08 g, 20.1 mmol). LC-MS:  $t_R = 0.65$  min,  $[M+1]^+ = 249$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.37-7.30 (m, 1H), 7.21-7.17 (m, 1H), 7.08-7.03 (m, 2H), 3.96 (s, 2H), 3.50 (hept,  $J = 6.4$  Hz, 1H), 2.40 (s, 3H), 1.14 (d,  $J = 6.4$  Hz, 6H).

#### Scaffold 4



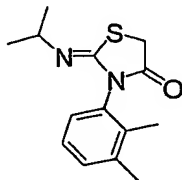
5

2-[(Z)-Isopropylimino]-3-p-tolyl-thiazolidin-4-one is obtained following Method A and starting from p-tolylisothiocyanate (3.0 g, 20.10 mmol), isopropylamine (1.19 g, 20.10 mmol), and methyl bromoacetate (3.08 g, 20.1 mmol).

10 LC-MS:  $t_R = 0.64$  min,  $[M+1]^+ = 249$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.28-7.24 (m, 2H), 7.16-7.12 (m, 2H), 3.96 (s, 2H), 3.50 (hept,  $J = 6.4$  Hz, 1H), 2.39 (s, 3H), 1.14 (d,  $J = 6.4$  Hz, 6H).

#### Scaffold 5



15

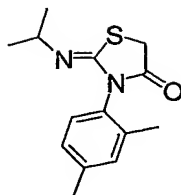
2-[(Z)-Isopropylimino]-3-(2,3-dimethylphenyl)-thiazolidin-4-one is obtained following Method A and starting from 2,3-dimethylphenylisothiocyanate (3.0 g, 18.38 mmol), isopropylamine (1.09 g, 18.38 mmol), and methyl bromoacetate (2.81 g, 18.38 mmol).

20

LC-MS:  $t_R = 0.74$  min,  $[M+1]^+ = 263$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.22-7.14 (m, 2H), 6.98-6.93 (m, 1H), 3.98 (s, 2H), 3.48 (hept,  $J = 6.4$  Hz, 1H), 2.32 (s, 3H), 2.02 (s, 3H), 1.10 (d,  $J = 6.4$  Hz, 6H).

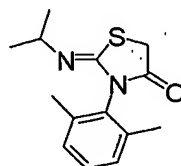
25

Scaffold 6

2-[(Z)-isopropylimino]-3-(2,4-dimethylphenyl)-thiazolidin-4-one is obtained following Method A and starting from 2,4-dimethylphenylisothiocyanate (3.0 g, 18.38 mmol), isopropylamine (1.64 g, 27.57 mmol), and methyl bromoacetate (2.81 g, 18.38 mmol).

LC-MS:  $t_R = 0.75$  min,  $[M+1]^+ = 263$ .

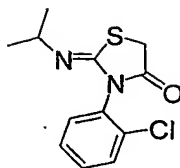
$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.12-7.06 (m, 2H), 6.98 (d,  $J = 8.2$  Hz, 1H), 3.98 (s, 2H), 3.49 (hept,  $J = 6.0$  Hz, 1H), 2.35 (s, 3H), 2.12 (s, 3H), 1.12 (d,  $J = 5.9$  Hz, 3H), 1.11 (d,  $J = 6.4$  Hz, 3H).

Scaffold 7

2-[(Z)-isopropylimino]-3-(2,6-dimethylphenyl)-thiazolidin-4-one is obtained following Method A and starting from 2,6-dimethylphenylisothiocyanate (3.0 g, 18.38 mmol), isopropylamine (1.09 g, 18.38 mmol), and methyl bromoacetate (2.81 g, 18.38 mmol).

LC-MS:  $t_R = 0.80$  min,  $[M+1]^+ = 263$ .

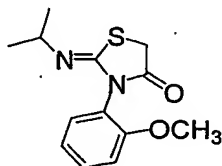
$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.24-7.10 (m, 3H), 4.00 (s, 2H), 3.48 (hept,  $J = 6.4$  Hz, 1H), 2.14 (s, 6H), 1.10 (d,  $J = 6.4$  Hz, 6H).

Scaffold 8

2-[(Z)-Isopropylimino]-3-(2-chlorophenyl)-thiazolidin-4-one is obtained following Method A and starting from 2-chlorophenylisothiocyanate (3.0 g, 17.68 mmol), isopropylamine (1.04 g, 17.68 mmol), and methyl bromoacetate (2.70 g, 17.68 mmol).

LC-MS:  $t_R = 0.81$  min,  $[M+1]^+ = 269$ .

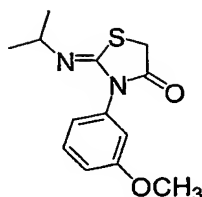
$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.53-7.48 (m, 1H), 7.40-7.34 (m, 2H), 7.30-7.24 (m, 1H), 4.07-3.93 (m, 2H), 3.48 (hept,  $J = 6.4$  Hz, 1H), 1.11 (d,  $J = 6.4$  Hz, 3H), 1.10 (d,  $J = 6.4$  Hz, 3H).

Scaffold 9

2-[(Z)-Isopropylimino]-3-(2-methoxyphenyl)-thiazolidin-4-one is obtained following Method A and starting from 2-methoxyphenylisothiocyanate (3.0 g, 18.16 mmol), isopropylamine (1.08 g, 18.16 mmol), and methyl bromoacetate (2.78 g, 18.16 mmol).

LC-MS:  $t_R = 0.62$  min,  $[M+1]^+ = 265$ .

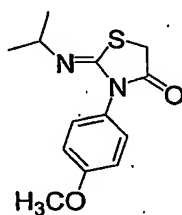
$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.42-7.35 (m, 1H), 7.19-7.14 (m, 1H), 7.06-6.98 (m, 2H), 3.80 (s, 3H), 3.55-3.42 (m, 1H), 1.11 (t, 5.9 Hz, 6H).

Scaffold 10

2-[(Z)-Isopropylimino]-3-(3-methoxyphenyl)-thiazolidin-4-one is obtained following  
 5 Method A and starting from 3-methoxyphenylisothiocyanate (3.0 g, 18.16 mmol),  
 isopropylamine (1.08 g, 18.16 mmol), and methyl bromoacetate (2.78 g, 18.16  
 mmol)

LC-MS:  $t_R = 0.65$  min,  $[M+1]^+ = 265$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.35 (t,  $J = 7.8$  Hz, 1H), 6.95-6.90 (m, 1H), 6.87-6.83 (m, 1H),  
 10 6.82-6.80 (m, 1H), 3.96 (s, 2H), 3.82 (s, 3H), 3.54-3.45 (m, 1H), 1.13 (d,  $J = 5.9$   
 Hz, 6H).

Scaffold 11

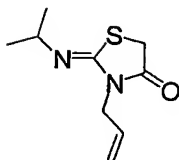
15

2-[(Z)-Isopropylimino]-3-(4-methoxyphenyl)-thiazolidin-4-one is obtained following  
 Method A and starting from 4-methoxyphenylisothiocyanate (3.0 g, 18.16 mmol),  
 isopropylamine (1.08 g, 18.16 mmol), and methyl bromoacetate (2.78 g, 18.16  
 mmol)

20 LC-MS:  $t_R = 0.62$  min,  $[M+1]^+ = 265$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.20-7.14 (m, 2H), 7.00-6.94 (m, 2H), 3.96 (s, 2H), 3.84 (s,  
 3H), 3.51 (hept,  $J = 6.4$  Hz, 1H), 1.14 (d,  $J = 6.4$  Hz, 6H).

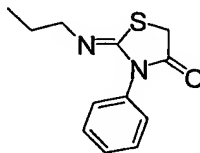
25

Scaffold 12

2-[(Z)-isopropylimino]-3-allyl-thiazolidin-4-one is obtained following Method A and starting from allylthiocyanate (5.95 g, 60 mmol), isopropylamine (3.55 g, 60 mmol), and methyl bromoacetate (9.18 g, 60 mmol).

LC-MS:  $t_R = 0.55$  min,  $[M+1]^+ = 199$

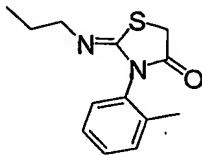
$^1H$  NMR ( $CDCl_3$ ):  $\delta$  5.82-5.69 (m, 1H), 5.10-5.02 (m, 2H), 4.17-4.13 (m, 2H), 4.01 (s, 2H), 3.39 (hept,  $J = 6.1$  Hz, 1H), 1.10 (d,  $J = 5.9$  Hz, 6H).

Scaffold 13

3-Phenyl-2-[(Z)-propylimino]-thiazolidin-4-one is prepared as described in Method

B. LC-MS:  $t_R = 0.60$  min,  $[M+1]^+ = 235$

$^1H$  NMR ( $CDCl_3$ ):  $\delta$  7.51-7.36 (m, 3H), 7.28-7.24 (m, 2H), 3.99 (s, 2H), 3.27 (t,  $J = 7.0$  Hz, 2H), 1.60 (hex,  $J = 7.0$  Hz, 2H), 0.91 (t,  $J = 7.6$  Hz, 3H).

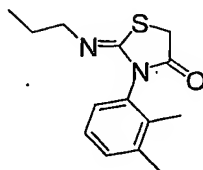
Scaffold 14

2-[(Z)-Propylimino]-3-o-tolyl-thiazolidin-4-one is obtained following Method B and starting from toluidine (2.21g, 20.6 mmol), chloroacetyl chloride (2.32 g, 20.6 mmol) and n-propylisothiocyanate (1.62 g, 16.0 mmol).

LC-MS:  $t_R = 0.68$  min,  $[M+1]^+ = 249$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.34-7.26 (m, 3H), 7.14-7.09 (m, 1H), 4.01 (s, 2H), 3.34-3.18 (m, 2H), 2.18 (s, 3H), 1.58 (hept,  $J = 7.0$  Hz, 2H), 0.88 (t,  $J = 7.0$  Hz, 3H).

#### Scaffold 15



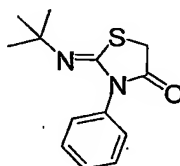
5

2-[(Z)-Propylimino]-3-(2,3-dimethylphenyl)-thiazolidin-4-one is obtained following Method B and starting from 2,3-dimethylaniline (3.36 g, 27.8 mmol), chloroacetyl chloride (3.14 g, 27.7 mmol) and n-propylisothiocyanate (2.05 g, 20.2 mmol).

10 LC-MS:  $t_R = 0.71$  min,  $[M+1]^+ = 263$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.22-7.16 (m, 2H), 6.98-6.94 (m, 1H), 4.00 (s, 2H), 3.34-3.18 (m, 2H), 2.32 (s, 3H), 2.05 (s, 3H), 1.57 (hex,  $J = 7.3$  Hz, 2H), 0.88 (t,  $J = 7.6$  Hz, 3H).

#### 15 Scaffold 16

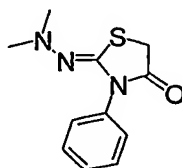


2-[(Z)-tert.-Butylimino]-3-phenylthiazolidin-4-one is obtained following Method A and starting from phenylisothiocyanate (2.03 g, 15.0 mmol), isopropylamine (0.887 g, 15.0 mmol), and methyl bromoacetate (2.29 g, 15.0 mmol).

20

LC-MS:  $t_R = 0.68$  min,  $[M+1]^+ = 249$ .

#### Scaffold 17

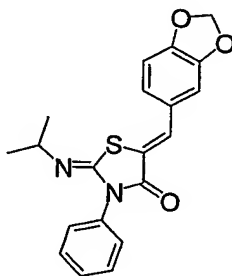


2-[(Z)-(Dimethyl-hydrazono)]-3-phenyl-thiazolidin-4-one is obtained following Method A and starting from phenylisothiocyanate (4.05 g, 30.0 mmol), dimethylhydrazine (asym.) (1.80 g, 30.0 mmol), and methyl bromoacetate (4.59 g, 30.0 mmol).

5 LC-MS:  $t_R = 0.69$  min,  $[M+1]^+ = 236$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.50-7.36 (m, 3H), 7.32-7.28 (m, 2H), 3.82 (s, 2H), 2.48 (s, 6H).

### Example 1



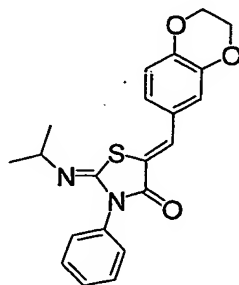
10

5-Benzo[1,3]dioxol-5-ylmeth-(Z)-ylidene-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one is prepared as described in Method C.

LC-MS:  $t_R = 1.06$  min,  $[M+1]^+ = 367$ .

15  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.70 (s, 1H), 7.52-7.32 (m, 5H), 7.12-7.07 (m, 2H), 6.92 (d,  $J = 7.6$  Hz, 1H), 6.06 (s, 2H), 3.61 (hept,  $J = 6.1$  Hz, 1H), 1.21 (d,  $J = 6.4$  Hz, 6H).

### Example 2

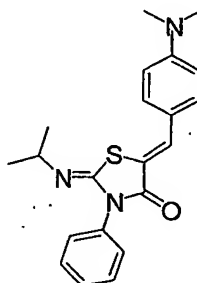


20 5-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmeth-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one is obtained starting from Scaffold 1 (19 mg, 0.08 mmol)

and 2,3-dihydro-benzo[1,4]dioxine-6-carbaldehyde (26 mg, 0.16 mmol) following Method E.

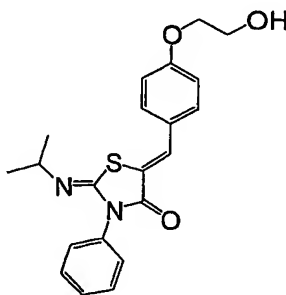
LC-MS:  $t_R = 1.05$  min,  $[M+1]^+ = 381$ .

### 5 Example 3



5-(4-Dimethylamino-benz-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one is obtained starting from Scaffold 1 (19 mg, 0.08 mmol) and 4-dimethylamino-benzaldehyde (24 mg, 0.16 mmol) following Method E. LC-MS:  $t_R = 1.09$  min,  $[M+1]^+ = 379$ .

### Example 4



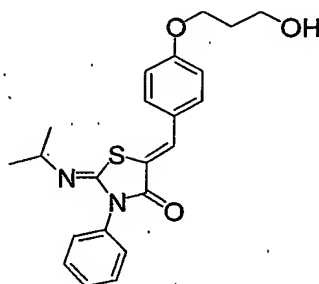
15

5-[4-(2-Hydroxy-ethoxy)-benz-(Z)-ylidene]-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one is prepared as described in Method D.

LC-MS:  $t_R = 0.94$  min,  $[M+1]^+ = 383$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.74 (s, 1H), 7.56-7.44 (m, 4H), 7.42-7.32 (m, 3H), 7.04-6.99 (m, 2H), 4.17-4.13 (m, 2H), 4.03-3.97 (m, 2H), 3.60 (hept,  $J = 6.4$  Hz, 1H), 2.01 (s br, 1H), 1.19 (d,  $J = 6.4$  Hz, 6H).

## 5 Example 5

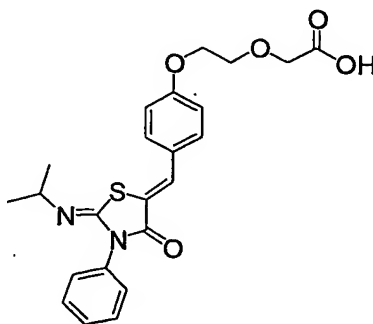


5-[4-(3-Hydroxy-propoxy)-benz-(Z)-ylidene]-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one is obtained starting from Scaffold 1 (150 mg, 0.640 mmol) and 4-(3-hydroxy-propoxy)-benzaldehyde (173 mg, 0.960 mmol) following Method D.

LC-MS:  $t_R = 0.97$  min,  $[M+1]^+ = 397$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.73 (s, 1H), 7.55-7.33 (m, 7H), 7.02-6.97 (m, 2H), 4.19 (t,  $J = 5.9$  Hz, 2H), 3.89 (t,  $J = 5.9$  Hz, 2H), 3.60 (hept,  $J = 6.4$  Hz, 1H), 2.09 (p,  $J = 5.9$  Hz, 2H), 1.19 (d,  $J = 6.4$  Hz, 6H).

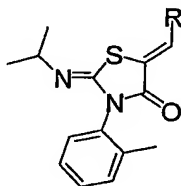
## Example 6



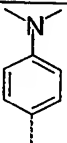
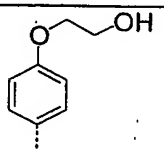
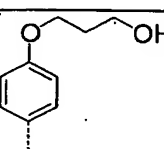
- A mixture of 5-[4-(2-Hydroxy-ethoxy)-benz-(Z)-ylidene]-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one (75 mg, 0.196 mmol, Example 4),  $K_2CO_3$  (81 mg, 0.588 mmol), and methyl chloroacetate (250 L) in DMF (2 mL) is stirred at 60°C for 96 h before it is diluted with EA (75 mL) and washed with 10% aq. citric acid (50 mL) and water (2x50 mL). The organic layer is evaporated and the resulting residue is purified by prep. TLC (heptane/EA 1:1) followed by crystallisation from a small amount of methanol to give {2-[4-(2-[(Z)-isopropylimino]-4-oxo-3-phenyl-thiazolidin-5-ylidene-methyl)-phenoxy]-ethoxy}-acetic acid.
- LC-MS:  $t_R = 1.06$  min,  $[M+1]^+ = 441$ .
- 10  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  7.73 (s, 1H), 7.55-7.44 (m, 4H), 7.42-7.32 (m, 3H), 7.03-6.98 (m, 2H), 4.55-4.50 (m, 2H), 4.29-4.25 (m, 2H), 3.83 (s, 2H), 3.60 (hept,  $J = 6.4$  Hz, 1H), 1.19 (d,  $J = 6.4$  Hz, 6H).

#### Examples 7 to 10

- 15 Starting from Scaffold 2, the following examples are prepared:



Example	R	Method	Scale (mmol)	LC-MS	
				$t_R$	$[M+1]^+$
7		C	0.604	1.10	381
8		E	0.200	1.09	395

9		C	0.604	1.03	380
10		D	0.400	0.98	397
11		D	0.604	1.01	411

Example 7

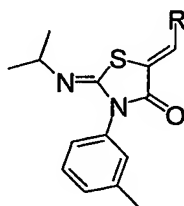
<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.69 (s, 1H), 7.34-7.27 (m, 3H), 7.20-7.14 (m, 1H), 7.12-7.07 (m, 2H), 6.91 (d, J = 7.6 Hz, 1H), 6.06 (s, 2H), 3.58 (hept, J = 6.4 Hz, 1H), 2.19 (s, 3H), 1.18 (d, J = 5.9 Hz, 3H), 1.17 (d, J = 5.9 Hz, 3H).

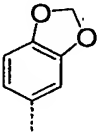
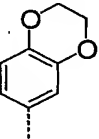
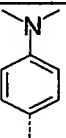
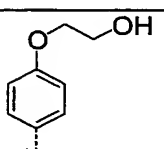
Example 11

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.73 (s, 1H), 7.55-7.50 (m, 2H), 7.35-7.27 (m, 3H), 7.20-7.15 (m, 1H), 7.02-6.98 (m, 2H), 4.20 (t, J = 5.9 Hz, 2H), 3.88 (t, J = 5.9 Hz, 2H), 3.58 (hept, J = 6.4 Hz, 1H), 2.18 (s, 3H), 2.09 (p, J = 5.9 Hz, 2H), 1.17 (d, J = 6.4, 3H), 1.16 (d, J = 6.4 Hz, 3H).

Examples 12 to 15

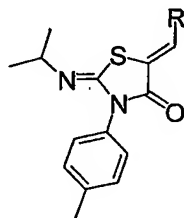
Starting from Scaffold 3, the following examples are prepared:

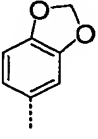


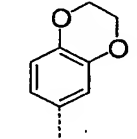
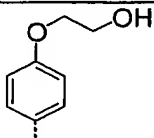
Example	R	Method	Scale (mmol)	LC-MS	
				$t_R$	$[M+1]^+$
12		E	0.200	1.08	381
13		E	0.200	1.08	395
14		E	0.200	1.01	380
15		D	0.400	0.97	397

### Examples 16 to 18

Starting from Scaffold 4, the following examples have been prepared:

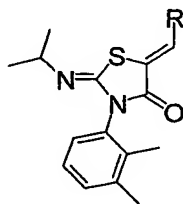


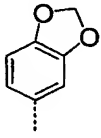
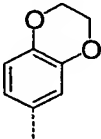
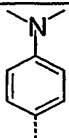
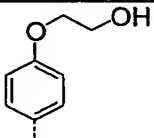
Example	R	Method	Scale (mmol)	LC-MS	
				$t_R$	$[M+1]^+$
16		E	0.200	1.09	381

17		E	0.200	1.09	395
18		D	0.400	0.97	397

Examples 19 to 22

Starting from Scaffold 5, the following examples have been prepared:



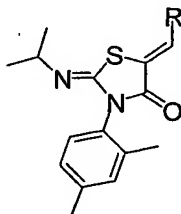
Example	R	Method	Scale (mmol)	LC-MS	
				$t_R$	$[M+1]^+$
19		E	0.200	1.11	395
20		E	0.200	1.11	409
21		E	<del>0.200</del>	1.05	394
22		D	0.763	0.99	411

Example 22

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.73 (s, 1H), 7.56-7.51 (m, 2H), 7.24-7.18 (m, 2H), 7.06-7.00 (m, 3H), 4.18-4.14 (m, 2H), 4.04-3.98 (m, 2H), 3.50 (hep,  $J = 6.4$  Hz, 1H), 2.35 (s, 3H), 2.05 (s, 3H), 2.00 (s br, 1H), 1.18 (d,  $J = 6.4$  Hz, 3H), 1.17 (d,  $J = 6.4$  Hz, 3H).

5 Examples 23 and 24

Starting from Scaffold 6, the following examples are prepared:



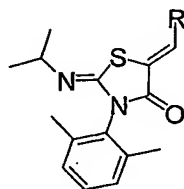
Example	R	Method	Scale (mmol)	LC-MS	
				$t_R$	$[M+1]^+$
23		E	0.200	1.12	409
24		D	0.762	1.00	411

Example 24

- 10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.72 (s, 1H), 7.56-7.50 (m, 2H), 7.14-6.98 (m, 5H), 4.17-4.12 (m, 2H), 4.02-3.96 (m, 2H), 3.58 (hept,  $J = 6.2$  Hz, 1H), 2.37 (s, 3H), 2.14 (s, 3H), 2.04 (s br, 1H), 1.17 (d,  $J = 6.2$  Hz, 3H), 1.16 (d,  $J = 6.2$  Hz, 3H).

Examples 25 to 26

Starting from Scaffold 7, the following examples are prepared:



Example	R	Method	Scale (mmol)	LC-MS	
				$t_R$	$[M+1]^+$
25		E	0.200	1.13	409
26		D	0.762	1.02	411

5

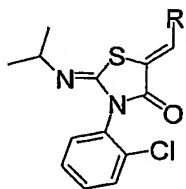
Example 26

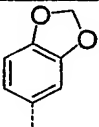
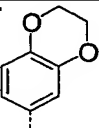
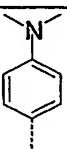
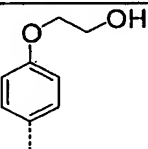
$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.73 (s, 1H), 7.57-7.52 (m, 2H), 7.27-7.21 (m, 1H), 7.17-7.12 (m, 2H), 7.04-6.99 (m, 2H), 4.18-4.13 (m, 2H), 4.03-3.98 (m, 2H), 3.57 (hept,  $J = 6.1$  Hz, 1H), 2.15 (s, 6H), 2.01 (s br, 1H), 1.16 (d,  $J = 6.4$  Hz, 6H).

10

Examples 27 to 30

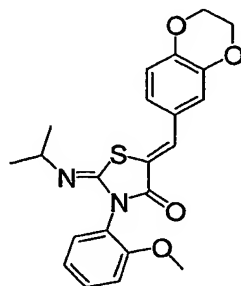
Starting from Scaffold 8, the following examples are prepared:



Example	R	Method	Scale (mmol)	LC-MS	
				$t_R$	$[M+1]^+$
27		E	0.200	1.11	401
28		E	0.200	1.11	415
29		E	0.200	1.09	400
30		D	0.744	0.99	417

Example 30

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.74 (s, 1H), 7.56-7.50 (m, 3H), 7.41-7.32 (m, 3H), 7.04-7.00 (m, 2H), 4.18-4.13 (m, 2H), 4.04-3.98 (m, 2H), 3.58 (hept,  $J = 6.1$  Hz, 1H), 2.01 (s  
5 br, 1H), 1.17 (d,  $J = 5.9$  Hz, 3H), 1.16 (d,  $J = 6.4$  Hz, 3H).

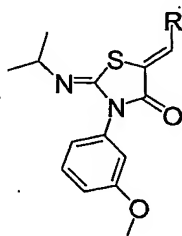
Example 31

5-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmeth-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-(2-  
10 methoxyphenyl)-thiazolidin-4-one is obtained starting from Scaffold 9 (53 mg,

0.200 mmol) and 2,3-dihydro-benzo[1,4]dioxine-6-carbaldehyde (49 mg, 0.300 mmol) following Method C. LC-MS:  $t_R = 1.03$  min,  $[M+1]^+ = 411$ .

### Examples 32 and 33

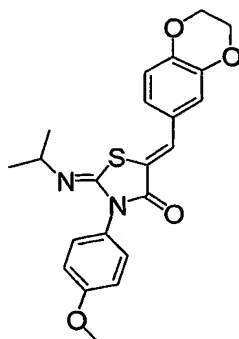
5 Starting from Scaffold 10, the following examples are prepared:



Example	R	Method	Scale (mmol)	LC-MS	
				$t_R$	$[M+1]^+$
32		E	0.200	1.06	411
33		D	0.380	0.95	413

10

### Example 34

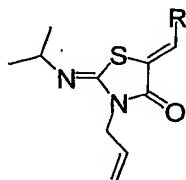


5-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmeth-(Z)-ylidene)-2-[(Z)-isopropylimino]-3-(4-methoxy-phenyl)-thiazolidin-4-one is obtained starting from Scaffold 11 (53 mg, 0.200 mmol) and 2,3-dihydro-benzo[1,4]dioxine-6-carbaldehyde (33 mg, 0.200 mmol) following Method E.

5 LC-MS:  $t_R = 1.05$  min,  $[M+1]^+ = 411$ .

### Example 35 to 38

Starting from Scaffold 12, the following examples are prepared:



10

Example	R	Method	Scale (mmol)	LC-MS	
				$t_R$	$[M+1]^+$
35		E	0.200	1.07	331
36		E	0.080	1.05	345
37		C	20.0	0.99	330.2
38		D	0.757	0.94	347

**Example 37**

$^1\text{H}$  NMR ( $\text{D}_6\text{-DMSO}$ ):  $\delta$  7.55 (s, 1H), 7.46-7.42 (m, 2H), 6.82-6.76 (m, 2H), 5.90-5.76 (m, 1H), 5.13-5.02 (m, 2H), 4.36-4.27 (m, 2H), 3.50 (hept,  $J = 6.0$  Hz, 1H), 2.99 (s, 6H), 1.16 (d,  $J = 5.9$  Hz, 6H).

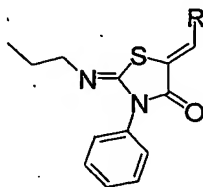
5

**Example 38**

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.66 (s, 1H), 7.51-7.46 (m, 2H), 7.01-6.96 (m, 2H), 5.96-5.83 (m, 1H), 5.28-5.14 (m, 2H), 4.49-4.44 (m, 2H), 4.16-4.12 (m, 2H), 4.03-3.96 (m, 2H), 3.55 (hept,  $J = 6.1$  Hz, 1H), 2.01 (t br,  $J = 5$  Hz, 1H), 1.24 (d,  $J = 5.9$  Hz, 6H).

10 **Examples 39 to 41**

Starting from Scaffold 13, the following examples are prepared:



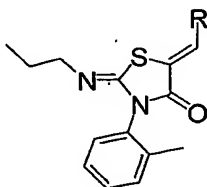
Example	R	Method	Scale (mmol)	LC-MS	
				$t_R$	$[M+1]^+$
39		C	0.640	1.06	367
40		C	0.333	1.05	381
41		D	0.854	0.95	383

Example 41

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.74 (s, 1H), 7.56-7.44 (m, 4H), 7.43-7.32 (m, 3H), 7.03-6.98 (m, 2H), 4.18-4.13 (m, 2H), 4.04-3.96 (m, 2H), 3.38 (t,  $J = 6.6$  Hz, 2H), 2.01 (s br, 1H), 1.72-1.59 (m, 2H), 0.95 (t,  $J = 7.6$  Hz, 3H).

5 Example 42 to 45

Starting from Scaffold 14, the following examples are prepared:



Example	R	Method	Scale (mmol)	LC-MS	
				$t_R$	$[M+1]^+$
42		C	0.805	1.08	381
43		C	0.805	1.08	395
44		D	0.805	0.96	397
45		D	0.427	0.99	411

Example 44

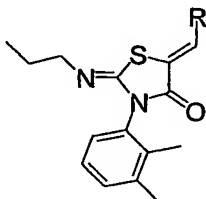
$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.74 (s, 1H), 7.57-7.52 (m, 2H), 7.36-7.28 (m, 3H), 7.20-7.16 (m, 1H), 7.05-7.00 (m, 2H), 4.18-4.14 (m, 2H), 4.04-3.98 (m, 2H), 3.46-3.30 (m, 2H), 2.20 (s, 3H), 2.00 (s br, 1H), 1.68-1.56 (m, 2H), 0.93 (t,  $J = 7.0$  Hz, 3H).

5 Example 45

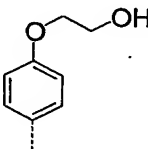
$^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.74 (s, 1H), 7.56-7.51 (m, 2H), 7.35-7.28 (m, 3H), 7.20-7.15 (m, 1H), 7.03-6.98 (m, 2H), 4.20 (t,  $J = 5.9$  Hz, 2H), 3.89 (t,  $J = 5.9$  Hz, 2H), 3.49-3.30 (m, 2H), 2.20 (s, 3H), 2.15-2.03 (m, 2H), 1.68-1.55 (m, 2H), 0.92 (t,  $J = 7.6$  HZ, 3H).

10 Example 46 to 48

Starting from Scaffold 15, the following examples are prepared:



Example	R	Method	Scale (mmol)	LC-MS	
				$t_R$	$[M+1]^+$
46		C	0.762	1.09	395
47		C	0.762	1.10	409

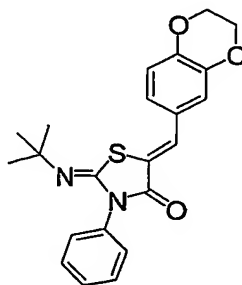
48		D	0.762	0.98	411
----	---	---	-------	------	-----

Example 46

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.69 (s, 1H), 7.23-7.18 (m, 2H), 7.13-7.08 (m, 2H), 7.04-7.00 (m, 1H), 6.93-6.90 (m, 1H), 6.06 (s, 2H), 3.46-3.30 (m, 2H), 2.34 (s, 3H), 2.07 (s, 3H), 1.70-1.55 (m, 2H), 0.92 8t, J = 7.6 Hz, 3H).

Example 48

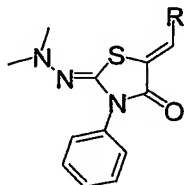
<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.74 (s, 1H), 7.57-7.52 (m, 2H), 7.23-7.20 (m, 2H), 7.05-7.00 (m, 3H), 4.18-4.14 (m, 2H), 4.03-3.98 (m, 2H), 3.48-3.30 (m, 2H), 2.35 (s, 3H), 2.07 (s, 3H), 1.67-1.57 (m, 2H), 0.93 (t, J = 7.6 Hz, 3H).

Example 49

5-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmeth-(Z)-ylidene)-2-tert-butylimino-3-(4-methoxy-phenyl)-thiazolidin-4-one is obtained starting from Scaffold 16 (20 mg, 0.08 mmol) and 2,3-dihydro-benzo[1,4]dioxine-6-carbaldehyde (26 mg, 0.16 mmol) following Method E. LC-MS: t<sub>R</sub> = 1.11 min, [M+1]<sup>+</sup> = 395.

Example 50 to 52

Starting from Scaffold 17, the following examples are prepared:



5

Example	R	Method	Scale (mmol)	LC-MS	
				$t_R$	$[M+1]^{++}$
50		C	0.850	1.06	368
51		E	0.08	1.04	382
52		D	0.850	0.95	384

Example 50

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.68 (s, 1H), 7.53-7.35 (m, 5H), 7.14-7.10 (m, 2H), 6.92-6.88 (m, 1H), 6.05 (s, 2H), 2.60 (s, 6H).

10

Example 51

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.65 (s, 1H), 7.54-7.35 (m, 5H), 7.15-7.09 (m, 2H), 6.94 (d,  $J = 8.2$  Hz, 1H), 4.35-4.29 (m, 4H), 2.58 (s, 6H).

Example 52

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.74 (s, 1H), 7.58-7.35 (m, 7H), 7.04-6.99 (m, 2H), 4.17-4.13 (m, 2H), 4.03-3.98 (m, 2H), 2.62 (s, 6H), 2.00 (s br, 1H).

5

Biological AssaysExample 53

The immunosuppressive activity of the compounds of the invention can be demonstrated by measuring the number of circulating lymphocytes in whole blood of rats as follows.

10

Normotensive male Wistar rats are housed in climate-controlled conditions with a 12-hour light/dark cycle, and have free access to normal rat chow and drinking water. Blood (0.5 mL) is collected by retro-orbital sampling before drug administration, and 3 and 6 h thereafter. Blood cell count is measured in whole blood using a Beckman-Coulter Synchron CX5 Pro cytometer. Statistical analysis of lymphocyte counts are performed by analysis of variance (ANOVA) using Statistica (StatSoft) and the Student-Newman-Keuls procedure for multiple comparisons.

15

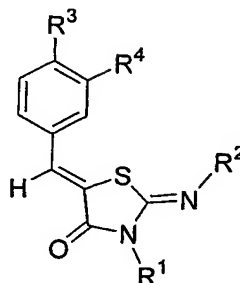
20

Thus, compounds of the invention decrease the number of circulating lymphocytes in whole blood when compared to pre-drug values.

**Claims**

1. Pharmaceutical composition containing at least one thiazolidin-4-one derivative of the General Formula (I)

5



General Formula (I)

wherein:

10

R<sup>1</sup> represents lower alkyl, lower alkenyl; lower alkynyl; cycloalkyl,  $\alpha$ -naphthyl;  $\beta$ -naphthyl; 5,6,7,8-tetrahydronaphth-1-yl; 5,6,7,8-tetrahydronaphth-2-yl; a phenyl group; a phenyl group independently mono-, di- or trisubstituted with lower alkyl, halogen, lower alkoxy, -CF<sub>3</sub>, or -CN;

15

R<sup>2</sup> represents lower alkyl; allyl, cyclopropyl, cyclobutyl; cyclopentyl; mono- or di-lower alkylamino;

R<sup>3</sup> represents -NR<sup>5</sup>R<sup>6</sup>; -O-CR<sup>7</sup>R<sup>8</sup>-CR<sup>9</sup>R<sup>10</sup>-(CR<sup>11</sup>R<sup>12</sup>)<sub>n</sub>-O-R<sup>13</sup>;

20

R<sup>4</sup> represents hydrogen; hydroxy; lower alkoxy; lower alkyl; halogen; or R<sup>3</sup> and R<sup>4</sup> together may form a methylenedioxy or ethylenedioxy ring which may be further substituted with a hydroxy methyl group;

25 R<sup>5</sup> and R<sup>6</sup> each represents independently lower alkyl;

R<sup>7</sup> represents hydrogen, lower alkyl or hydroxymethyl; R<sup>7</sup> and R<sup>9</sup> together with the carbon atoms to which they are attached may form a five- or six-membered saturated carbocyclic ring; in case n represents the integer 1, R<sup>7</sup> and R<sup>11</sup> together with the carbon atoms to which they are attached may form a five- or six-  
5 membered saturated carbocyclic ring;

R<sup>8</sup>, R<sup>9</sup>, R<sup>11</sup> and R<sup>12</sup> each represents independently hydrogen or lower alkyl;

R<sup>10</sup> represents hydrogen or lower alkyl; in case n represents the integer 1, R<sup>10</sup> in  
10 addition represents lower alkoxy, hydroxy, -NH<sub>2</sub>, -NHR<sup>5</sup> or -NR<sup>5</sup>R<sup>6</sup>;

R<sup>13</sup> represents hydrogen; lower alkyl; hydroxycarbonyl-lower alkyl; -(CH<sub>2</sub>)<sub>2</sub>-OH;  
1-glyceryl or 2-glyceryl;

15 n represents the integer 0 or 1;

and configurational isomers, optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form, as well as  
20 pharmaceutically acceptable salts, solvent complexes, and morphological forms, and inert carrier material.

2. Pharmaceutical composition according to claim 1 in which said thiazolidin-  
4-one derivatives is the (Z, Z)-isomer.

25

3. Pharmaceutical composition according to claim 1 or 2 for the prevention or treatment of disorders associated with an activated immune system.

4. Pharmaceutical composition according to any of claims 1 to 3 for the  
30 prevention or treatment of organ transplant rejection or graft-versus-host diseases.

5. Pharmaceutical composition according to any of claims 1 to 4 for the prevention or treatment of diseases or disorders associated with an activated

immune system selected from the group consisting of autoimmune syndromes including rheumatoid arthritis; systemic lupus erythematosus; Hashimoto's thyroiditis; lymphocytic thyroiditis; multiple sclerosis; myasthenia gravis; type I diabetes; uveitis; posterior uveitis; uveitis associated with Behcet's disease;

5 uveomeningitis syndrome; allergic encephalomyelitis; chronic allograft vasculopathy; post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis; inflammatory and hyperproliferative skin diseases; psoriasis; atopic dermatitis; osteomyelitis; contact dermatitis; eczematous dermatitis; seborrheic dermatitis; lichen planus; pemphigus; bullous

10 pemphigoid; epidermolysis bullosa; urticaria; angioedema; vasculitis; erythema; cutaneous eosinophilia; acne; alopecia areata; keratoconjunctivitis; vernal conjunctivitis; keratitis; herpetic keratitis; dystrophia epithelialis corneae; corneal leukoma; ocular pemphigus; Mooren's ulcer; ulcerative keratitis; scleritis; Graves' ophthalmopathy; Vogt-Koyanagi-Harada syndrome; sarcoidosis; pollen allergies;

15 reversible obstructive airway disease; bronchial asthma; allergic asthma; intrinsic asthma; extrinsic asthma; dust asthma; chronic or inveterate asthma; late asthma and airway hyper-responsiveness; bronchitis; gastric ulcers; ischemic bowel diseases; inflammatory bowel diseases; necrotizing enterocolitis; intestinal lesions associated with thermal burns; coeliac diseases; proctitis; eosinophilic

20 gastroenteritis; mastocytosis; Crohn's disease; ulcerative colitis; vascular damage caused by ischemic diseases and thrombosis; atherosclerosis; fatty heart; myocarditis; cardiac infarction; arteriosclerosis; aortitis syndrome; cachexia due to viral disease; vascular thrombosis; migraine; rhinitis; eczema; interstitial nephritis; IgA-induced nephropathy; Goodpasture's syndrome; hemolytic-uremic syndrome;

25 diabetic nephropathy; glomerulosclerosis; glomerulonephritis; multiple myositis; Guillain-Barre syndrome; Meniere's disease; polyneuritis; multiple neuritis; mononeuritis; radiculopathy; hyperthyroidism; Basedow's disease; thyrotoxicosis; pure red cell aplasia; aplastic anemia; hypoplastic anemia; idiopathic thrombocytopenic purpura; autoimmune hemolytic anemia; agranulocytosis;

30 pernicious anemia; megaloblastic anemia; anerythroplasia; osteoporosis; sarcoidosis; fibroid lung; idiopathic interstitial pneumonia; dermatomyositis; leukoderma vulgaris; ichthyosis vulgaris; photoallergic sensitivity; cutaneous T cell lymphoma; polyarteritis nodosa; Huntington's chorea; Sydenham's chorea;

myocardosis; scleroderma; Wegener's granuloma; Sjogren's syndrome; adiposis; eosinophilic fascitis; lesions of gingiva, periodontium, alveolar bone, substantia ossea dentis; male pattern alopecia or alopecia senilis; muscular dystrophy; pyoderma; Sezary's syndrome; chronic adrenal insufficiency; Addison's disease;

5 ischemia-reperfusion injury of organs which occurs upon preservation; endotoxin shock; pseudomembranous colitis; colitis caused by drug or radiation; ischemic acute renal insufficiency; chronic renal insufficiency; lung cancer; malignancy of lymphoid origin; acute or chronic lymphocytic leukemias; lymphoma; psoriasis; pulmonary emphysema; cataracta; siderosis; retinitis pigmentosa; senile macular

10 degeneration; vitreal scarring; corneal alkali burn; dermatitis erythema; ballous dermatitis; cement dermatitis; gingivitis; periodontitis; sepsis; pancreatitis; carcinogenesis; metastasis of carcinoma; hypobaropathy; autoimmune hepatitis; primary biliary cirrhosis; sclerosing cholangitis; partial liver resection; acute liver necrosis; cirrhosis; alcoholic cirrhosis; hepatic failure; fulminant hepatic failure;

15 late-onset hepatic failure; "acute-on-chronic" liver failure.

6. Pharmaceutical composition according to claim 5, comprising disorders which are selected from the group consisting of autoimmune syndromes including rheumatoid arthritis, multiple sclerosis, myasthenia gravis; pollen allergies; type I

20 diabetes; prevention of psoriasis; Crohn's disease; post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis; and metastasis of carcinoma.

7. Use of one or more compound of the General Formula (I) in claim 1 for the

25 prevention or treatment of disorders associated with an activated immune system.

8. Use of one or more compound of the General Formula (I) in claim 1 for the prevention or treatment of organ transplant rejection or graft-versus-host diseases.

30 9. Use according to claim 7 comprising disorders which are selected from the group consisting of autoimmune syndromes including rheumatoid arthritis; systemic lupus erythematosus; Hashimoto's thyroiditis; lymphocytic thyroiditis; multiple sclerosis; myasthenia gravis; type I diabetes; uveitis; posterior uveitis;

uveitis associated with Behcet's disease; uveomeningitis syndrome; allergic encephalomyelitis; chronic allograft vasculopathy; post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis; inflammatory and hyperproliferative skin diseases; psoriasis; atopic dermatitis;

5 osteomyelitis; contact dermatitis; eczematous dermatitis; seborrhoeic dermatitis; lichen planus; pemphigus; bullous pemphigoid; epidermolysis bullosa; urticaria; angioedema; vasculitis; erythema; cutaneous eosinophilia; acne; alopecia areata; keratoconjunctivitis; vernal conjunctivitis; keratitis; herpetic keratitis; dystrophia epithelialis corneae; corneal leukoma; ocular pemphigus; Mooren's ulcer;

10 ulcerative keratitis; scleritis; Graves' ophthalmopathy; Vogt-Koyanagi-Harada syndrome; sarcoidosis; pollen allergies; reversible obstructive airway disease; bronchial asthma; allergic asthma; intrinsic asthma; extrinsic asthma; dust asthma; chronic or inveterate asthma; late asthma and airway hyper-responsiveness; bronchitis; gastric ulcers; ischemic bowel diseases; inflammatory bowel diseases;

15 necrotizing enterocolitis; intestinal lesions associated with thermal burns; coeliac diseases; proctitis; eosinophilic gastroenteritis; mastocytosis; Crohn's disease; ulcerative colitis; vascular damage caused by ischemic diseases and thrombosis; atherosclerosis; fatty heart; myocarditis; cardiac infarction; arteriosclerosis; aortitis syndrome; cachexia due to viral disease; vascular thrombosis; migraine; rhinitis;

20 eczema; interstitial nephritis; IgA-induced nephropathy; Goodpasture's syndrome; hemolytic-uremic syndrome; diabetic nephropathy; glomerulosclerosis; glomerulonephritis; multiple myositis; Guillain-Barre syndrome; Meniere's disease; polyneuritis; multiple neuritis; mononeuritis; radiculopathy; hyperthyroidism; Basedow's disease; thyrotoxicosis; pure red cell aplasia; aplastic anemia;

25 hypoplastic anemia; idiopathic thrombocytopenic purpura; autoimmune hemolytic anemia; agranulocytosis; pernicious anemia; megaloblastic anemia; anerythroplasia; osteoporosis; sarcoidosis; fibroid lung; idiopathic interstitial pneumonia; dermatomyositis; leukoderma vulgaris; ichthyosis vulgaris; photoallergic sensitivity; cutaneous T cell lymphoma; polyarteritis nodosa;

30 Huntington's chorea; Sydenham's chorea; myocardosis; scleroderma; Wegener's granuloma; Sjogren's syndrome; adiposis; eosinophilic fascitis; lesions of gingiva, periodontium, alveolar bone, substantia ossea dentis; male pattern alopecia or alopecia senilis; muscular dystrophy; pyoderma; Sezary's syndrome; chronic

adrenal insufficiency; Addison's disease; ischemia-reperfusion injury of organs which occurs upon preservation; endotoxin shock; pseudomembranous colitis; colitis caused by drug or radiation; ischemic acute renal insufficiency; chronic renal insufficiency; lung cancer; malignancy of lymphoid origin; acute or chronic lymphocytic leukemias; lymphoma; psoriasis; pulmonary emphysema; cataract; siderosis; retinitis pigmentosa; senile macular degeneration; vitreal scarring; corneal alkali burn; dermatitis erythema; bullous dermatitis; cement dermatitis; gingivitis; periodontitis; sepsis; pancreatitis; carcinogenesis; metastasis of carcinoma; hypobaropathy; autoimmune hepatitis; primary biliary cirrhosis; sclerosing cholangitis; partial liver resection; acute liver necrosis; cirrhosis; alcoholic cirrhosis; hepatic failure; fulminant hepatic failure; late-onset hepatic failure; "acute-on-chronic" liver failure.

10. Use according to claim 9 in which said disorders are selected from the group consisting of autoimmune syndromes including rheumatoid arthritis, multiple sclerosis, myasthenia gravis; pollen allergies; type I diabetes; prevention of psoriasis; Crohn's disease; post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis; and metastasis of carcinoma.

11. Use of one or more compounds of the General Formula (I) in claim 1 in combination with one or several immunosuppressant compounds for the treatment of disorders associated with an activated immune system.

12. Use according to claim 11 wherein said other immunosuppressant compound is selected from the group consisting of cyclosporin, daclizumab, basiliximab, everolimus, tacrolimus (FK506), azathioprine, leflunomide, 15-deoxyspergualin, or other immunosuppressant drugs.

13. A method for the prevention or treatment of disorders associated with an activated immune system comprising the administration to the patient of a pharmaceutical composition containing at least one compound of the General Formula (I) in claim 1.

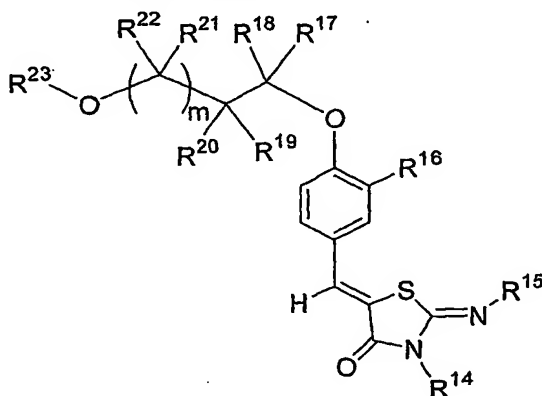
14. A method for the prevention or treatment of disorders of organ transplant rejection or graft-versus-host diseases comprising the administration to the patient of a pharmaceutical composition containing at least one compound of the General Formula (I) in claim 1.

15. A method according to claim 13 or 14 by administering to the patient a dose of the thiazolidin-4-one derivative of the General Formula (I) in claim 1 between 0.5 mg and 1000 mg per day.

16. A method according to claim 15 by administering to the patient a dose of the thiazolidin-4-one derivative of the General Formula (I) between 1 mg and 500 mg per day.

17. A method according to claim 16 by administering to the patient a dose of the thiazolidin-4-one derivative of the General Formula (I) between 5 mg and 200 mg per day.

18. Novel thiazolidin-4-one derivatives of the General Formula (II)



General Formula (II)

wherein:

$R^{14}$  represents lower alkyl, lower alkenyl; lower alkynyl; cycloalkyl;  $\alpha$ -naphthyl;  $\beta$ -naphthyl; 5,6,7,8-tetrahydronaphth-1-yl; 5,6,7,8-tetrahydronaphth-2-yl; a phenyl

group; a phenyl group mono-, di- or trisubstituted independently with lower alkyl, halogen, lower alkoxy,  $-CF_3$ , or  $-CN$ ;

5  $R^{15}$  represents lower alkyl; allyl; cyclopropyl; cyclobutyl; cyclopentyl; cycloalkyl-lower alkyl; mono- or di-lower alkylamino;

$R^{16}$  represents hydrogen; hydroxy; lower alkoxy; lower alkyl; or halogen;

10  $R^{17}$  represents hydrogen, lower alkyl, or hydroxymethyl;  $R^{17}$  and  $R^{19}$  together with the atoms to which they are attached may form a five- or six-membered carbocyclic saturated ring; in case m represents the integer 1,  $R^{17}$  and  $R^{21}$  together with the atoms to which they are attached may form a five- or six-membered carbocyclic saturated ring;

15  $R^{18}$ ,  $R^{19}$ ,  $R^{21}$  and  $R^{22}$  each represents independently hydrogen or lower alkyl;

$R^{20}$  represents hydrogen or lower alkyl; and in case m represents the integer 1,  $R^{20}$  in addition represents lower alkoxy, hydroxy,  $-NH_2$ ,  $-NHR^5$  or  $-NR^5R^6$ ;

20  $R^{23}$  represents hydrogen; lower alkyl; hydroxycarbonyl-lower alkyl;  $-(CH_2)_2-OH$ ; 1-glyceryl or 2-glyceryl;

m represents the integer 0 or 1;

25 and configurational isomers, optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form, as well as pharmaceutically acceptable salts.

30 19. Thiazolidin-4-one derivatives according to claim 18 in which said thiazolidin-4-one derivatives according to formula (II) are (Z,Z) isomers.

20. Thiazolidin-4-one derivatives according to claim 18 or 19 wherein  $R^{14}$  represents an unsubstituted, a mono- or disubstituted phenyl group.
21. Thiazolidin-4-one derivatives according to any of claims 18 to 20 wherein  $R^{15}$  represents lower alkyl.
22. Thiazolidin-4-one derivatives according to any of claims 18 to 21 wherein  $m$  represents the integer 0,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$  and  $R^{20}$  represent hydrogen.
23. Thiazolidin-4-one derivatives according to any of claims 18 to 22 wherein  $R^{23}$  represents hydrogen.
24. Thiazolidin-4-one derivatives according to any of claims 18 to 23 wherein  $R^{16}$  represents hydrogen, halogen or methyl.
25. Thiazolidin-4-one derivatives according to any of claims 18 to 24 wherein  $R^{14}$  represents an unsubstituted, a mono- or disubstituted phenyl group,  $R^{15}$  represents lower alkyl,  $m$  represents the integer 0,  $R^{16}$  represents hydrogen, halogen or methyl,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{23}$  each represent hydrogen.
26. Thiazolidin-4-one derivatives according to claim 18 or 19 wherein  $m$  represents the integer 1,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{21}$ ,  $R^{22}$ ,  $R^{23}$  represent hydrogen, and  $R^{20}$  represents hydroxy.
27. A thiazolidin-4-one derivative according to any of claims 18 to 26 selected from the group consisting of:
- 5-[4-(2-Hydroxy-ethoxy)-benz-(Z)-ylidene]-2-[(Z)-isopropylimino]-3-*o*-tolyl-thiazolidin-4-one;
- 3-(2,3-Dimethyl-phenyl)-5-[4-(2-hydroxy-ethoxy)-benz-(Z)-ylidene]-2-[(Z)-isopropylimino]-thiazolidin-4-one;

- 5-[4-(2-Hydroxy-ethoxy)-benz-(Z)-ylidene]-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one;
- 5 5-[3-Chloro-4-(2-hydroxy-ethoxy)-benz-(Z)-ylidene]-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one;
- 5-[3-Chloro-4-(2-hydroxy-ethoxy)-benz-(Z)-ylidene]-2-[(Z)-isopropylimino]-3-(2-methylphenyl)-thiazolidin-4-one;
- 10 5-[3-Chloro-4-(2-hydroxy-ethoxy)-benz-(Z)-ylidene]-3-(2,3-dimethyl-phenyl)-2-[(Z)-isopropylimino]-thiazolidin-4-one;
- 15 5-[4-(2-Hydroxy-ethoxy)-benz-(Z)-ylidene]-3-phenyl-2-[(Z)-propylimino]-thiazolidin-4-one;
- 5-[3-Chloro-4-(2-hydroxy-ethoxy)-benz-(Z)-ylidene]-3-(2,3-dimethyl-phenyl)-2-[(Z)-propylimino]-thiazolidin-4-one;
- 20 5-[3-Chloro-4-(2,3-dihydroxy-propoxy)-benz-(Z)-ylidene]-2-[(Z)-isopropylimino]-3-phenyl-thiazolidin-4-one;
- 5-[3-Chloro-4-(2,3-dihydroxy-propoxy)-benz-(Z)-ylidene]-2-[(Z)-isopropylimino]-3-otolyl-thiazolidin-4-one;
- 25 5-[3-Chloro-4-(2,3-dihydroxy-propoxy)-benz-(Z)-ylidene]-3-(2,3-dimethyl-phenyl)-2-[(Z)-isopropylimino]-thiazolidin-4-one;
- 30 5-[3-Chloro-4-(2,3-dihydroxy-propoxy)-benz-(Z)-ylidene]-3-phenyl-2-[(Z)-propylimino]-thiazolidin-4-one;
- 5-[3-Chloro-4-(2,3-dihydroxy-propoxy)-benz-(Z)-ylidene]-2-[(Z)-propylimino]-3-otolyl-thiazolidin-4-one;

5-[3-Chloro-4-(2,3-dihydroxy-propoxy)-benz-(Z)-ylidene]-3-(2,3-dimethyl-phenyl)-2-[(Z)-propylimino]-thiazolidin-4-one;

5 5-[3-Chloro-4-(2-hydroxy-ethoxy)-benz-(Z)-ylidene]-3-isopropyl-2-[(Z)-isopropyl-  
imino]-thiazolidin-4-one.

28. A thiazolidin-4-one derivative according to any of claims 18 to 27 for use as a medicament.

10 29. A process for the preparation of a pharmaceutical composition comprising a compound of the General Formula (II) in claim 18, characterized by mixing one or more active ingredients according to any one of claims 18 to 27 with inert excipients in a manner known *per se*.

15 30. A process for the preparation of a pharmaceutical composition comprising a compound of the General Formula (I) in claim 1, characterized by mixing one or more active ingredients according to General Formula (I) with inert excipients in a manner known *per se*.

**Abstract**

5 The invention relates to pharmaceutical compositions containing at least one thiazolidin-4-one derivative to prevent or treat disorders associated with an activated immune system. Furthermore, the invention relates to novel thiazolidin-4-one derivatives notably for use as pharmaceutically active compounds. Said compounds particularly act also as immunosuppressive agents.

**This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record.**

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☒ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**